In the specification:

At page 18, Table 1, for the control group (i.e. zero dosage), the number of rats should be 12, not 8 as stated. Therefore, under column 2 ("No. of rats"), row 1 ("None"), delete "8" and replace with --12--.

REMARKS

Status of the Application

To summarize the current status of the application, Claims 1-19 are pending. Claims 7-9 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-6 and 10-19 stand rejected.

Claim Rejections - 35 U.S.C. § 112

Claims 5-6, 13-14 and 18-19 have been rejected as being incomplete for omitting essential elements. Claims 5-6 have been amended to correct this error. It is believed that these amendments to Claims 5-6 overcome the rejection of Claims 13-14 and 18-19 as well.

Claim Objections

Claims 2-4, 10-12 and 15-17 have been objected to as being of improper dependent form. These claims, or the claims from which they depend, recite "a compound of formula I of claim 1", but the definition of the compound of the formula of claim I does not encompass the compounds recited in Claims 2-4, 10-12 and 15-17.

Applicants have amended Claims 2-4 (and, similarly, Claims

5-6) to place the claims in independent form. The amendments to Claims 2-4 and 5-6 (1) are supported throughout the specification but especially in Figure 2, and (2) do not introduce new matter which would require additional searching. The Examiner has already searched the compounds of amended Claims 2-4 and 5-6. For these reasons, Applicants submit that entry of these amendments to Claims 2-4 and 5-6 are proper at this time.

Rejection of Claims 1-6 and 10-14 under 35 U.S.C. § 103

Claims 1-6 and 10-14 continue to be rejected under 35 U.S.C. § 103 over (1) Holick et al. '538, (2) Holick et al. '643 and (3) Bishop et al. '429. Claims 1-4 and 10-12 continue to be rejected under 35 U.S.C. § 103 over Gulbrandsen et al. '790. Claims 15-19, added by Amendment A, are rejected under 35 U.S.C. § 103 over (1) Holick et al. '538, (2) Holick et al. '643 and (3) Bishop et al. '429. Claims 15-17 are also rejected under 35 U.S.C. § 103 over Gulbrandsen et al. '790.

The general basis for the Examiner's rejections in all instances is that one or more of the cited references discloses a "generic group of vitamin D derivatives" including the claimed 1α-hydroxyvitamin D_5 compounds. Applicants do not dispute that Holick et al. '538 discloses a generic group of vitamin D derivatives which includes Applicants' 1α-hydroxyvitamin D_5 compound. Likewise, Applicants do not dispute that the Examiner has raised a prima facie case of obviousness.

However, a prima facie case of obviousness may be rebutted with evidence that the claimed invention yields unexpectedly

improved properties or properties not present in the prior art. Rebuttal evidence may also consist of showing that the claimed compound possesses unexpected properties. MPEP §2144.08 II(B), citing Dillon, 919 F.2d at 692-93, 16 USPQ2d at 1901. "Differences in properties" may include "significant differences in degree of the same property amounting to a marked superiority" In re Hoch, 166 USPQ 406 (CCPA 1970).

Applicants respectfully traverse the Examiner's §103 rejections of the claims and herewith submit a declaration by one of the inventors, Dr. Robert Moriarty (Attachment A), as evidence that the claimed compound possesses a key unexpected property (reduced calcemic activity) amounting to a marked superiority over the prior art compounds, which not only renders Applicants' compound patentable, but makes it commercially promising for the prevention and treatment of cancer.

I. The Declaration of Dr. Robert Moriarty demonstrates the unexpectedly low calcemic activity of 1α-hydroxyvitamin D_5 compared to the closest prior art compounds.

The tendency of virtually all Vitamin D analogs to increase serum calcium is well known. Thus in Gulbrandsen et al. U.S. Patent No. 5,700,790, the authors state: "...1α,25-$(OH)_2$ Vitamin D_3 is known to be a potent stimulator of calcium absorption..." (Col. 2, lines 52-53). Holick et al. Patent No. 5,254,538 at col. 3, lines 11-14 states that topical application of vitamin D analogs may be an effective method of therapy for diseases involving calcium, phosphorus and bone metabolism problems. Knutson Patent No. 5,488,120 teaches that 1α(OH) Vitamin D_4 is

useful for the treatment of disorders of calcium metabolism. Data provided in Knutson indicates that 1α(OH) Vitamin D_4 is effective at increasing serum calcium in vitamin D deficient rats.

Based on its structural similarity to its vitamin D analogs, particularly 1α(OH) Vitamin D_4[1], one of ordinary skill in the art at the time of Applicants' invention would have predicted similar calcemic activity for the heretofore unknown compound 1α-hydroxyvitamin D_5. As Applicants have shown and will now explain in detail, this prediction is clearly erroneous.

As Table 1 in Dr. Moriarty's declaration shows, 1α-hydroxyvitamin D_5 is considerably less calcemic than its closest analogs: 1α(OH) Vitamin D_3, 1α,25-$(OH)_2$ Vitamin D_3 and 1α(OH) Vitamin D_4. For example, at a dosage of 0.042 μg/kg/day, the serum calcium level in vitamin D deficient rats receiving 1α-hydroxyvitamin D_5 was only 6.0 mg/100mL, compared to 9.0 mg/100mL for 1α(OH) Vitamin D_3, 8.1 mg/100mL for 1α,25-$(OH)_2$ Vitamin D_3 and 7.1 mg/100mL for 1α(OH) Vitamin D_4.

An even more dramatic difference is shown at a dosage of 0.25 μg/kg/day, where the serum calcium level in vitamin D deficient rats receiving 1α-hydroxyvitamin D_5 was found to be only 7.9 mg/100mL, compared to 12.0 mg/100mL for 1α(OH) Vitamin D_3, 10.1 mg/100mL for 1α,25-$(OH)_2$ Vitamin D_3 and 11.6 mg/100mL for 1α(OH) Vitamin D_4.

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[1] 1α(OH) vitamin D_4 and 1α-hydroxyvitamin D_5 differ only at the C24 carbon, where 1α(OH) Vitamin D_4 possesses an (S) methyl group and 1α-hydroxyvitamin D_5 possesses an (R) ethyl group.

The fact that applicants' 1α-hydroxyvitamin D_5 compound actually has substantially lower calcemic activity than its vitamin D analogs was unexpected based on literature precedence and compels a finding of patentability.

In the final Office Action the Examiner notes that "the prior art indicated that the compounds have a tendency or inability to cause hypercalcemia and/or hypercalciuria (see Bishop, col. 5, lines 60-67)." From this passage in Bishop the Examiner appears to conclude that "[o]ne of ordinary skill in the art would expect compounds having similar structure to those taught by Bishop to have similar properties and, thus, a lower tendency or inability to cause hypercalcemia and/or hypercalciuria as taught by the prior art."

While this passage in Bishop may suggest that structures of Formula I have a lower tendency or inability to cause hypercalcemia, Bishop does not teach or suggest that one of those structures, 1α-hydroxyvitamin D_5, has a substantially lower calcemic activity than the others.

Thus, based on this statement in Bishop, one of ordinary skill in the art would not necessarily expect that 1α-hydroxyvitamin D_5 to have a substantially lower tendency or inability to cause hypercalcemia than 1α(OH) Vitamin D_3, 1α,25-$(OH)_2$ Vitamin D_3 or 1α(OH) Vitamin D_4. The fact that 1α-hydroxyvitamin D_5 is substantially less calcemic than these structurally similar compounds was surprising and unexpected at the time of Applicants' invention.

II. The data provided by applicants is a true side-by-side comparison of applicants' compound with the closest prior art.

In the final Office Action, the Examiner stated that the "applicant's showing of unexpected results is not a true side-by-side comparison of the closest prior art compound with the claimed compounds and, thus is not persuasive." In the declaration submitted herewith, Dr. Moriarty attests to the fact that the comparison provided in the specification and elaborated on in Dr. Moriarty's declaration is indeed a true side-by-side comparison obtained by the same researcher (Dr. Joyce Knutson, Director of Preclinical Research at Lunar Corporation, Madison, Wisconsin) in the same lab.

In addition to the side-by-side comparison of the claimed compound with the closest prior art compounds, Dr. Moriarty's declaration summarizes the experimental protocol used, the number of animals tested, the type and weight of the animals, the dosage amounts, the experimental controls, the materials and methods used, and the numerical results including standard deviations. Applicants submit that the information provided by Dr. Moriarty provides a sound scientific basis for evaluating Applicants' contention that the calcemic activity of 1α-hydroxyvitamin D_5 was substantially and unexpectedly lower than that of the prior art compounds.

III. Secondary considerations - Long felt but unmet need

For nearly twenty years researchers have focused on more than 1,200 forms of vitamin D_3 as an anticarcinogen, but have

been frustrated because the various forms of vitamin D_3 also lead to harmful increases in serum calcium levels. Applicants' claimed compound has great potential to fulfill this long felt but unmet need for a form of vitamin D useful in the prevention of and treatment of cancer. When the present inventors published their results in the Journal of the National Cancer Institute[2], the editorial board of the Journal had this to say:

> "A major focus of chemopreventive research in the field of vitamin D and cancer has been to synthesize analogues of 1α,25-$(OH)_2$ Vitamin D_3 that have prominent antiproliferative effects against cancer cells without resulting in hypercalcemia when they are administered in vivo at pharmacologically active doses....The study by Mehta et al. reported in this issue of the Journal presents an entirely novel class of vitamin D compounds (vitamin D_5). Utilizing a mammary gland lesion model to assess chemoprevention, the authors demonstrated preventive effects in vitro but no significant effects on serum calcium levels in vivo. Thus, the therapeutic index (ratio of its proliferative to its calcemic effects) for this compound is sufficiently high to warrant further investigations..." J. National Cancer Inst. 1997; 89(3) at 182-83 (Attachment C)

Since this editorial, Applicants have conducted cell culture studies with 1α-hydroxyvitamin D_5 and have received funding from the U.S. Army to conduct preclinical toxicity and Phase I trials. The studies indicate that 1α-hydroxyvitamin D_5 inhibits tumor incidence at a non-toxic concentration. Applicants have submitted a manuscript to the Journal of the National Cancer Institute entitled "Prevention of N-methyl-N-nitrosourea-induced mammary carcinogenesis in rats by 1α-hydroxyvitamin D_5" by Mehta et al. (Attachment D), which is currently under consideration for

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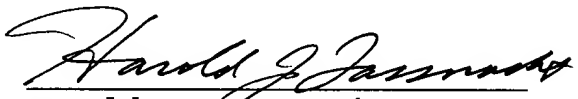
[2] A reprint of the article is part of the record, but is included here as Attachment B for convenience.

publication.

Summary

The amendments to the claims made herein were made to comply with requirements as to form expressly set forth in the previous Office Action. The amendment to the specification was made to correct an inadvertent error in Table 1. For the reasons provided above, Applicants submit that Claims 1-6 and 10-19 are in condition for allowance. Applicants requests that this Amendment be entered, and that Claims 1-6 and 10-19 be allowed.

Respectfully submitted,



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